Independent Prognostic Value of MRproANP (Midregional Proatrial Natriuretic Peptide) Levels in Patients With Stroke Is Unaltered Over Time

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Abstract: Background and Purpose- MRproANP (midregional proatrial natriuretic peptide) is known to be independently associated with cardioembolic stroke cause and to improve risk stratification for 90-day mortality when measured within 24 to 72 hours after symptom onset in patients with acute ischemic stroke. However, the optimal time point for assessment remains unclear. This study aimed to evaluate prognostic utility of MRproANP at different time points during the first 5 days of hospitalization in patients with acute ischemic stroke. Methods- Samples of MRproANP were collected on admission (<72 hours after onset) and at multiple time points during the first 5 days of hospitalization in 348 consecutively enrolled patients with acute ischemic stroke. The prognostic value for 90-day mortality, 90-day functional outcome, and the association with cardioembolic stroke cause was assessed regarding the time of measurement, and change over time was modeled using generalized estimating equations. Results- MRproANP levels modestly decease over the initial 5 days but remain highly predictive for cardioembolic stroke cause (odds ratio, 9.75 [95% CI, 3.2-29]; 10.62 [95% CI, 3.4-33.3]; 10.8 [95% CI, 3.1-37.1]; 19.4 [95% CI, 5.49-68.7] on admission, day 1, 3 and 5) and 90-day mortality (odds ratio, 59.4 [95% CI, 7.4-480.7]; 78.3 [95% CI, 7.9-772.6]; 14.5 [95% CI, 1.4-145]; 19.81 [95% CI, 2.7-143.4] on admission, day 1, 3, and 5). Change over time does not significantly modify the prognostic value of MRproANP (P=0.65 and P=0.56 for the interaction term in the multivariate model). Conclusions- Independent prognostic value of MRproANP remains unaltered in the acute phase of stroke at least up to 5 days; repeated measurements do not improve the prognostic value.

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Independent prognostic value of MRproANP levels in stroke patients is unaltered over time

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Abstract

Background and Purpose: Midregional proatrial natriuretic peptide (MRproANP) is known to be independently associated with cardioembolic (CE) stroke etiology and to improve risk stratification for 90-day mortality when measured within 24-72h after symptom onset in acute ischemic stroke (AIS) patients. However, the optimal time-point for assessment remains unclear. This study aimed to evaluate prognostic utility of MRproANP at different time-points during the first 5 days of hospitalization in AIS patients.

Methods: Samples of MRproANP were collected on admission (< 72h after onset) and at multiple time-points during the first 5 days of hospitalization in 348 consecutively enrolled AIS patients. The prognostic value for 90-day mortality, 90-day functional outcome and the association with CE stroke etiology was assessed regarding the time of measurement and change over time was modeled using generalized estimating equations (GEE).

Results: MRproANP levels modestly decease over the initial 5 days but remain highly predictive for CE stroke etiology (OR: 9.75 [95% CI: 3.2–29]; 10.62 [3.4–33.3]; 10.8 [3.1–37.1]; 19.4 [5.49–68.7] on admission, day 1, 3 and 5) and 90-day mortality (OR 59.4 [7.4–480.7]; 78.3 [7.9–772.6]; 14.5 [1.4–145]; 19.81 [2.7–143.4] on admission, day 1, 3 and 5). Change over time does not significantly modify the prognostic value of MRproANP (p=0.65 and p=0.56 for the interaction term in the multivariate model).

Conclusion: Independent prognostic value of MRproANP remains unaltered in the acute phase of stroke at least up to 5 days; repeated measurements do not improve the prognostic value.

Introduction

In patients with acute ischemic stroke (AIS) blood biomarkers have the potential to provide objective, reliable and timely information in addition to clinical assessments. Midregional proatrial natriuretic peptide (MRproANP) is the prohormone fragment of ANP, a vasoactive hormone synthesized in atrial cardiac tissue and secreted in response to stretching forces. It was shown to improve risk stratification for 90-day mortality and to be associated with cardioembolic (CE) stroke etiology when measured up to 72h after symptom onset, thus MRproANP may facilitate the selection of patients for prolonged cardiac monitoring or anticoagulation in the future[1]. However, little is known about the short-time dynamics of MRproANP in the acute setting of stroke, thus optimal time-point for the assessment remains unknown. The aim of this study was to characterize the time-course of MRproANP in AIS during the first 5 days and assess its prognostic value concerning CE stroke etiology, 90-day mortality and functional outcome at different time-points.

Methods

The data supporting the findings of this study are available from the corresponding author on reasonable request. The local Ethics Committee approved the study protocol and informed consent was obtained from all patients. A detailed methods section is available in the online-only supplement.

Briefly, we analyzed data of a prospective cohort study. 348 participants with the diagnosis of AIS were included for longitudinal biomarker analysis. Patients that did not survive the first 5 days (n=11) were excluded (Figure I of the supplementary material). Baseline characteristics, comorbidities and neurological deficits were recorded on admission. Stroke etiology was determined after standardized diagnostic

workup and patients were followed-up for 90 days. Blood samples were taken on admission, day 1, 3 and 5, respectively. We performed binary logistic regression analysis controlled for age and 2 to 3 main predictors to evaluate the association of MRproANP at different time-points with the predefined outcomes. To assess whether MRproANP remains a clinically relevant predictor we compared receiver operating characteristic (ROC) curves for models with and without MRproANP. Further, we used a generalized estimating equations (GEE) model with an interaction-term for time of measurement to asses if there is a change in the prognostic value over time.

Results

Baseline characteristics of the full cohort (n=359) are summarized in Table I of the supplementary material. Median age was 75 years, 42% of participants where female, 12% deceased within the first 90-days, 42% had an unfavorable outcome. In 36% of cases etiological workup revealed CE stroke etiology (detailed description is available in Table II of the supplemental material). Blood samples were available on admission, day one (87.9%), three (76.7%) and five (74.7%), respectively. Overall, MRproANP levels significantly differed between the first 5 days ($p<0.001$) with the highest values on admission. The 11 patients excluded from biomarker analysis due to lack of repeated measurements were significantly older (85 vs 75 years), had higher NIHSS (21 vs 5 points) and a higher rate of TACS (63% vs 8%) than the remaining cohort (Table III of the supplementary material).

On all time-points MRproANP levels were significantly higher in CE stroke patients, patients with unfavorable outcome and patients who died within 90 days (Figure 1).

MRproANP and cardioembolic stroke: Logistic regression analysis revealed that the association of MRproANP with cardioembolic stroke etiology remained stable over the period of 5 days independent of age, history of heart failure and AF (OR: 9.75 [95% CI: 3.2–29]; 10.62 [95% CI: 3.4–33.3]; 10.8 [95% CI: 3.1–37.1]; 19.4 [95% CI: 5.49–68.7] on admission, day 1, day 3 and day 5 respectively).

ROC analysis of the prediction model for CE stroke etiology showed that MRproANP significantly improves the prediction model at every time-point ($p < 0.001$) (Figure II and Table IV of the supplementary material). To further evaluate the association of MRproANP trajectories and CE stroke etiology, we used GEE to model the change of MRproANP. Interaction terms of MRproANP and time of measurement revealed no significant difference in the prognostic value ($p=0.65$ in the final model).

MRproANP and functional outcome: In logistic regression MRproANP was associated with unfavorable outcome at every time-point (OR: 7.89 [95% CI: 3.62–17.18]; 12.54 [95% CI: 5.1–30.3]; 10.4 [95% CI: 4–26.9]; OR 6.54 [95% CI: 2.7–15.8] on admission, day 1, day 3 and day 5) but did not remain an independent predictor after adjusting for main predictors (CCI, NIHSS and TACS). In the GEE model, interaction analysis revealed no significant change in the prognostic ability over time ($p=0.56$ in the final model).

MRproANP and mortality*:* After adjusting for age, congestive heart failure and the two main predictors for mortality (TACS and NIHSS on admission), MRproANP remained a strong independent predictor for 90 day mortality (OR 59.4 [95% CI: 7.4–480.7]; 78.3 [95% CI: 7.9–772.6]; 14.5 [95% CI: 1.4–145]; 19.81 [95% CI: 2.7–143.4] on admission, day 1, day 3 and day 5) respectively. MRproANP significantly improved the model at every time-point ($p<0.001$ on admission and day 1, $p<0.05$ on

days 3, p<0.01 on day 5) (Figure II and Table IV of the supplementary material). GEE model again showed no significant change in the prognostic ability over time (p=0.56 in the final model).

Additional interaction analysis for Body Mass Index (BMI) which is known to influence MRproANP levels did not show any significant interaction (p=0.21; p=0.13; p= 0.26 for CE stroke, functional outcome and mortality).

Discussion

It has previously been shown that MRproANP is associated with the predefined outcomes when single-sampled in AIS patients[1, 2], however the short-time release kinetics of MRproANP in the immediate aftermath of AIS have not been described. Yet, it has been demonstrated that MRproANP levels can change rapid enough to be followed in the acute setting of stroke[3] and that repeated measurements of MRproANP can improve the diagnostic and prognostic utility in other disease settings[4, 5].

In contrast, our data shows that the prognostic value of MRproANP for the reported outcomes remains unaltered in the acute phase of stroke. While the crude odds differed between time-points, stable AUCs suggesting that there is no preferred time-point for the assessment. In addition, using GEE modeling, MRproANP change over time revealed no significant difference in the prognostic utility. Thus, we concluded that there is no benefit in repeated measurements and that early as well as later measures will provide similar prognostic information. However, the underlying pathophysiological mechanisms which are responsible for the observed release kinetiks are not fully understood yet. Especially, it remains unclear to what extend MRproANP levels reflect underlying cardiac disease already present before the event

or a disturbance in neuro-cardiac control as a reaction to the event. It has been shown that stroke location correlates with post-stoke biomarker changes and occurrence of post stroke arrhythmias[6, 7] supporting the hypothesis of an autonomic connection between the brain and heart. On the other hand MRproANP was shown to independently predict ischemic stroke and AF when measured in stroke free individuals[8, 9] suggesting that MRproANP levels also reflect preexisting cardiac disease. Further studies are needed to elucidate the complex interplay between MRproANP levels, cardiac function, stroke-risk and mortality. Our study has several limitations. First, it is a single-center study, thus it needs to be externally validated. Second, due to the longitudinal design there has been a number of missing MRproANP values due to missed blood draws, transfer to referring primary care hospitals and rehabilitation centers or early discharges. To account for this fact we applied GEE models which are robust to missing data. Despite these limitations our study represents the first study to evaluate repeated measurements of MRproANP in AIS.

Conclusion

The prognostic value of MRproANP for mortality, 90-day functional outcome and cardioembolic stroke etiology remains stable over the short period of 5 days in AIS patients. Analysis of the time-course of MRproANP does not support a preferred time-point for assessment or additional value of repeated measurements.

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Disclosures:

Dr. Luft recieves personal fees from AMGEN outside the submitted work.

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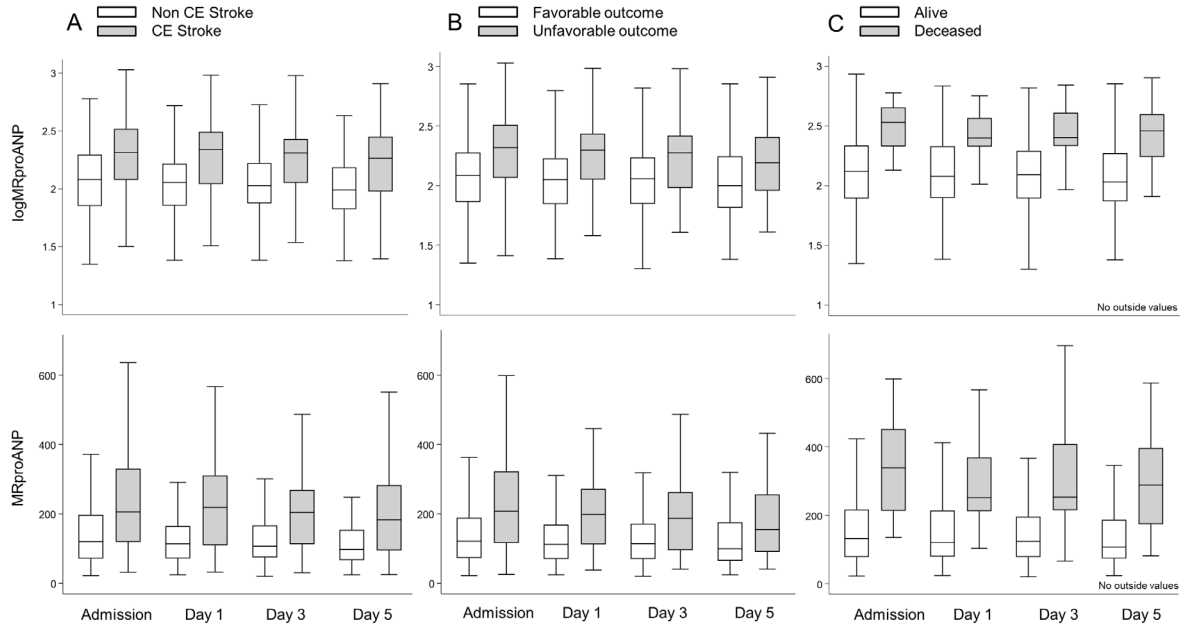
Figure 1 – Boxplot of MRproANP levels at different time-points in regard to outcome variables



A Association of MRproANP with cardioembolic (CE) stroke etiology. B Association of MRproANP with 90-day functional outcome. C Association of MRproANP with 90-day mortality.

SUPPLEMENTAL MATERIAL

Methods

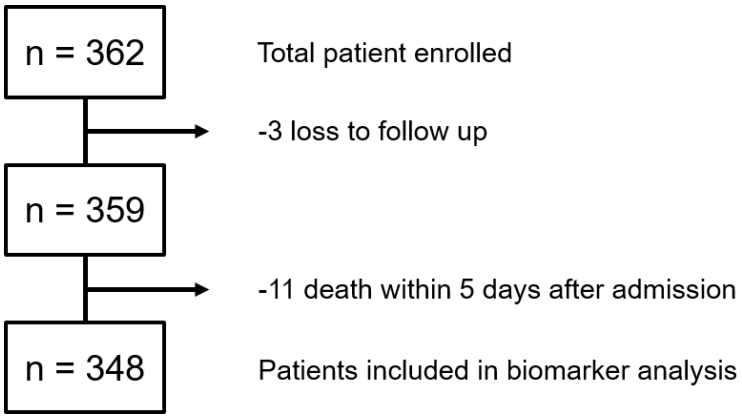
Study design: To assess the short-time trajectories of MRproANP we analyzed data of a prospective cohort study as described in detail elsewhere[1]. Briefly, a total of 605 consecutive patients with a suspected cerebrovascular event were initially enrolled within 72h from symptom onset. 359 patients had a diagnosis of AIS defined according to the World Health Organization criteria and completed 90 day follow up. For the longitudinal biomarker analysis, we included 348 participants. Patients that did not survive the first 5 days after admission (n=11) had to be excluded since repeated measurements of MRproANP were not possible and missing values were not considered as missing at random. Baseline characteristics including demographic variables and comorbidities were recorded on admission by patient history and review of discharge letters. Relevant comorbidities were assessed by the Charlson comorbidity index (CCI) adjusted for stroke[2]. Hypertension was defined as blood pressure above 140/90 mmHg repeatedly or currently under medical treatment with antihypertensive agents. Dyslipidemia was defined as low density lipoprotein (LDL) levels above 2,6mmol/L or currently under medical treatment with lipid-lowering drugs. Active smoking status was defined as current smoking or stopped within the previous 2 years. A positive family history was defined as a cardiovascular event (stroke or myocardial infarction) in a first grade relative aged ≤ 65 years. Congestive heart failure was defined as exertional or paroxysmal nocturnal dyspnea that has responded to treatment. Neurological deficits on admission were assessed by a stroke neurologist using the National Institute of Health Stroke Scale (NIHSS). Stroke etiology was determined according to the TOAST (trial of Org 10172 in Acute Stroke Treatment) classification at discharge. All patients underwent standardized diagnostic workup including brain computer-tomography (CT), magnet resonance imaging (MRI), or both; standard 12-lead ECG; 24-h-ECG; echocardiography; and neurosonographic examination. The clinical stroke syndrome was determined applying the criteria of the Oxfordshire Community Stroke Project [3]. Mortality and functional outcome according to the modified Ranking Scale (mRS) was assessed via a structured telephone interview on day 90, blinded to MRproANP levels. A favorable outcome was defined as a mRS score of 0 to 2. The local Ethics Committee approved the study protocol (EKBB#157/06) and informed consent was obtained from all patients. Anonymized study data is available on reasonable request.

Sample Processing: Blood samples were available on admission and on day 1, 3 and 5 respectively. Blood was collected in EDTA containing plastic tubes, centrifuged locally at 3000g at 4° C for 20 minutes and plasma was immediately aliquoted and frozen at -80°C. MRproANP was measured in a blinded batch analysis with a sandwich immunoassay (BRAHMS AG, Henningsdorf,

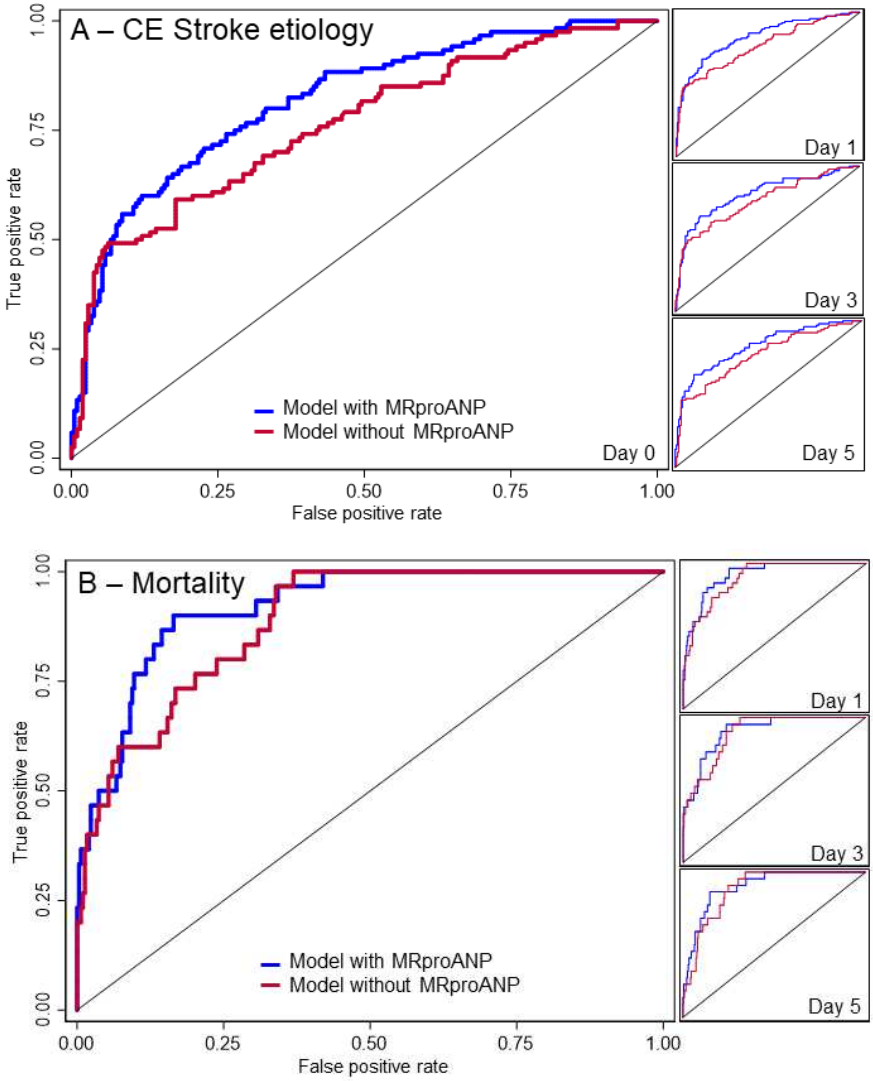
Germany) as described in detail elsewhere [4]. Three hundred twenty-eight patients (93.4%) had at last two separate measurements during the course of the study.

Statistical Analysis: Discrete variables are summarized as counts (percentages) and continuous variables as medians (interquartile ranges [IQR]) in the baseline characteristics. For two group comparisons, Fisher's exact test and Mann–Whitney U test was used depending on the variable type. Common logarithmic transformation (base 10) was performed to transform to normality for skewed distributions (e.g. MRproANP levels). Skillings–Mack test for repeated measures with missing data was used to assess MRproANP changes over time in a non-parametric fashion. To evaluate the association of logMRproANP measured at different time-points with CE etiology, 90-day functional outcome and 90-day mortality binary logistic regression analysis was performed. We controlled for age and 2 to 3 main predictors depending on the outcome variable to avoid overfitting (i.e. congestive of heart failure and atrial fibrillation (AF) for CE stroke etiology; NIHSS, Charlson Comorbidity Index (CCI) and total anterior circulation syndrome (TACS) for 90-day functional outcome; TACS, NIHSS and congestive heart failure for 90-day mortality). Receiver Operating Characteristic (ROC) curves and the area under the ROC curve (AUC) were calculated for the models with and without logMRproANP. The likelihood ratio test was used to compare nested vs the respective whole models (including logMRproANP) at each time-point, in order to assess whether MRproANP remains an independent and clinically relevant predictor during the observational period. Further, to account for within subject correlation and the unequal number of repeated measurements in the same individuals over time we used a generalized estimating equations (GEE) model with a probit link for the binary outcomes. Since GEE models are robust to errors in specification of the correlation structure [5] all models were fitted using an independent correlation structure. To asses if there is a change in the prognostic value over time, we included an interaction term for logMRproANP and the time of measurement. GEE models were performed with logMRproANP alone and with age and the two main predictors for each outcome as specified above. Because of the potential influence of body mass index (BMI) on MRproANP levels we performed additional interaction analysis for BMI and logMRproANP in bivariate and multivariate GEE models. P-values < 0.05 were considered statistically significant. Data analysis was performed using STATA version 15 (StataCorp LLC, College Station, Texas).

Supplementary Figure I – Study flow chart



Supplementary Figure II – Receiver operating characteristic curve for models in- and excluding logMRproANP levels according to outcome variables.



A – ROC curves of the nested model 1 including age, congestive heart failure and known atrial fibrillation (AF) (red line) and model 2 inlcuding age, congestive heart failure, AF and logMRproANP (blue line) with cardioembolic (CE) stroke etiology as the outcome variable. B – ROC curves of the nested model 1 including age, NIHSS, total anterior circulation syndrom (TACS) and congestive heart failure (red line) and model 2 inlcuding age, NIHSS, TACS, congestive heart failure and logMRproANP (blue line) with 90-day mortality as the outcome variable.

Supplementary Table I – Baseline Characteristics

		Stroke Etiology			Functional Outcome			Mortality at 90 days		
	All	**CE stroke**	**Non CE stroke**	**p Value**	**mRS 0-2**	**mRS 3-6**	**p Value**	**Alive**	**Dead**	**p Value**
n (%)	359 (100)	131 (36)	228 (64)	-	208 (58)	151 (42)	-	315 (88)	44 (12)	-
Demographics										
Age*, median (IQR)	75 (63-83)	76 (65-82)	75 (62-83)	0.43	71 (59-80)	80 (71-86)	**< 0.001**	74 (61-82)	83 (78-87)	**< 0.001**
Female sex, n (%)	149 (42)	60 (46)	89 (39)	0.22	75 (50)	74 (36)	**< 0.01**	128 (40)	21(48)	0.42
Medical history										
Arterial hypertension, n (%)	275 (77)	106 (81)	169 (74)	0.16	152 (73)	123 (81)	0.08	238 (76)	37 (84)	0.26
Smoking status, n (%)	124 (35)	42 (32)	82 (36)	0.49	79 (38)	45 (30)	0.12	113 (36)	11 (25)	0.18
Diabetes mellitus, n (%)	71(20)	24 (18)	47 (21)	0.68	39 (19)	32 (21)	0.59	62 (20)	9 (20)	0.84
Family history of vascular events, n (%)	106 (30)	37 (28)	69 (30)	0.72	67 (32)	39 (26)	0.2	94 (30)	12 (27)	0.86
Congestive heart failure, n (%)	54 (15)	31 (24)	23 (10)	**< 0.001**	21 (10)	33 (21)	**< 0.01**	42 (13)	12 (27)	**0.02**
Dyslipidemia, n (%)	93 (26)	31 (24)	62 (27)	0.53	58 (28)	35 (23)	0.33	82 (26)	11 (25)	1
Coronyry artery disease, n (%)	91 (25)	38 (29)	53 (23)	0.26	48 (23)	43 (29)	0.27	74 (24)	17 (39)	**0.04**
Prior Stroke, n (%)	88 (25)	32 (24)	56 (25)	0.54	48 (23)	40 (26)	0.45	80 (25)	8 (18)	0.35
Atrial fibrillation, n (%)	75 (21)	62 (47)	13 (6)	**< 0.001**	41 (27)	34 (16)	**0.02**	18 (41)	57 (18)	**0.001**
Charlson Index[&], median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.1	0 (0-2)	1 (0-2)	**< 0.001**	1 (0-2)	1 (0-2)	0.09
BMI [£], median (IQR)	25.4 (23-28)	24.8 (22-28)	25.5 (23-8)	0.28	24.5 (21-27)	25.7 (24-28)	**<0.05**	25.5 (23-28)	23.1 (21-26)	**< 0.001**
Stroke Syndrome, n (%)										
PACS	162 (45)	72 (55)	90 (39)	**< 0.01**	92 (44)	70 (46)	0.74	144 (46)	18 (41)	0.62
TACS	41 (11)	19 (15)	22 (10)	0.17	11 (5)	30 (20)	**< 0.001**	25 (8)	16 (36)	**< 0.001**
LACS	74 (21)	16 (12)	58 (25)	0.003	47 (23)	27 (18)	0.29	70 (22)	4 (9)	**0.05**
POCS	82 (23)	24 (18)	58 (25)	0.15	58 (28)	24 (16)	0.008	76 (24)	6 (14)	0.13
Stroke severity										
NIHSS, median (IQR)	5 (2-10)	6 (3-13)	5 (2-9)	**0.03**	4 (2-6)	8 (4-17)	**<0.001**	4 (2-8)	17.5 (8.5-25)	**<0.001**
Laboratory, median (IQR)										
Creatinine (umol/L)[¶]	76 (63-90)	77 (64-91)	75 (63-88)	0.52	76 (64-89)	76 (63-91)	0.92	75 (62-88)	81 (64-99)	0.19
MRproANP Admission[§] (pmol/L)	143 (83-238)	206 (120-326)	125 (72-207)	**< 0.001**	122 (73-189)	213 (119-333)	**< 0.001**	132 (78-217)	345 (228-465)	**< 0.001**
MRproANP Day 1[§] (pmol/L)	131 (84-228)	219 (116-311)	115 (72-172)	**< 0.001**	112 (70-169)	212 (116-291)	**< 0.001**	120 (79-214)	288 (214-415)	**< 0.001**
MRproANP on Day 3[§] (pmol/L)	135 (81 – 213)	204 (113-270)	107 (75-169)	**< 0.001**	114 (70-172)	188 (96-264)	**< 0.001**	124 (78-196)	259 (215-410)	**< 0.001**
MRproANP on Day 5[§] (pmol/L)	113 (77 – 204)	184 (95-283)	98 (67-1255)	**< 0.001**	100 (65-176)	155 (83-256)	**< 0.001**	107 (74-187)	300 (174-433)	**< 0.001**

Values are median (IQR) or counts (%) (* age was missing in 0,3%; § MRproANP values were missing in 6,4% on admission, 13% on day 1, 26% on day 3 and 27% on day 5); ¶ creatinine values were missing on 2,5% on admission; [&]charlson index values were missing in 0,8% on admission; [£]BMI was missing in 12% on admission). P-Values were assessed using the Fisher's exact test and Mann–Whitney U test depending on the variable type. IQR = interquartile range; LACS = lacunar syndrome; NIHSS = National Institutes of Health Stroke Scale; PACS = partial anterior circulation syndrome; POCS = posterior circulation syndrome; TACS = total anterior circulation syndrome; BMI = body mass index

Supplementary Table II – Observed sources of cardiac embolism in TOAST 2 classified strokes

Cardioembolic Stroke, n (%)	131
Known atrial fibrillation	62 (47)
Newly diagnosed atrial fibrillation during hospitalisation	23 (18)
Patent foramen ovale and / or septal aneurysm	20 (15.5)
Congestive heart failure	8 (6)
Atrial flutter	2 (1.5)
Other *	16 (12)

* includes high-risk sources (mechanical prosthetic valve, left atrial / ventricular thrombus, sick sinus syndrome, recent myocardial infarction, dilatated cardiomyopathy, atrial myxoma, endocarditis) and medium-risk sources (mitral valve prolaps, mitral anulus calcification, mitral stenosis, bioprosthetic cardiac valve, local hypokinetic segment) of cardioembolism.

Supplementary Table III – Comparison of baseline characteristics between analysed subset and excluded patients

	Full cohort	**Analysed subset**	**Excluded Patients**	**p-value**
n (%)	359 (100)	348 (97)	11 (3)	-
Demographics				
Age, median (IQR)	75 (63-83)	75 (63 – 82)	85 (81-90)	**< 0.001**
Female sex, n (%)	149 (42)	144 (41)	5 (45)	0.77
Medical history				
Arterial hypertension, n (%)	275 (77)	165 (76)	10 (91)	0.47
Smoking status, n (%)	124 (35)	122 (35)	2 (18)	0.34
Diabetes mellitus, n (%)	71 (20)	70 (20)	1 (9)	0.7
Family history of vascular events, n (%)	106 (30)	106 (30)	3 (27)	1
Congestive heart failure, n (%)	54 (15)	50 (14)	4 (36)	0.07
Dyslipidemia, n (%)	93 (26)	92 (26)	1 (9)	0.3
Coronary artery disease, n (%)	91 (25)	87 (25)	4 (36)	0.48
Prior Stroke, n (%)	88 (25)	85 (24)	3 (27)	0.74
Charlson Index, median (IQR)	1 (0-2)	1 (0-2)	1 (1-2)	0.36
BMI, median (IQR)	25.4 (23-27.8)	22 (21.1-26.8)	25.4 (23-27.8)	0.1
Stroke Syndrome, n (%)				
PACS	162 (45)	160 (46)	2 (18)	0.12
TACS	41 (11)	34 (10)	7 (64)	**< 0.001**
LACS	74 (21)	73 (21)	1 (9)	0.47
POCS	82 (23)	81 (23)	1 (9)	0.47
Stroke severity				
NIHSS, median (IQR)	5 (2-10)	5 (2-10)	21 (11-26)	**< 0.001**
Laboratory				
Creatinine (µmol/L), median (IQR)	76 (63-89.5)	76 (63-89)	89 (68-133)	0.1

Values are median (IQR) or counts (%). P-values were assessed using the Fisher's exact test and Mann–Whitney U test depending on the variable type. IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; BMI = body mass index; LACS = lacunar syndrome; PACS = partial anterior circulation syndrome; POCS = posterior circulation syndrome; TACS = total anterior circulation syndrome.

Supplementary Table Table IV – Overview of Areas Under the Receiver Operating Characteristic curves.

Prediction Model	AUC (95% CI)			
	logMRproANP alone	Model 1	Model 2	P value
CE Stroke Etiology				
Admission	0.70 (0.63-0.75)	0,76 (0.71-0.82)	0,82 (0.77-0.87)	**< 0.001**
Day 1	0.72 (0.66-0.78)	0,77 (0.71-0.83)	0,82 (0.78-0.88)	**< 0.001**
Day 3	0.71 (0.64-0.77)	0,76 (0.7-0.82)	0,81 (0.75-0.87)	**< 0.001**
Day 5	0.70 (0.63-0.77)	0,76 (0.7-0.82)	0,83 (0.77-0.88)	**< 0.001**
90-day Functional Outcome				
Admission	0.68 (0.62-0.74)	0.82 (0.78-0.88)	0.83 (0.78-0.87)	0.70
Day 1	0.70 (0.64-0.76)	0.84 (0.79-0.89)	0.84 (0.80-0.89)	0.17
Day 3	0.68 (0.61-0.75)	0.80 (0.75-0.86)	0.81 (0.75-0.86)	0.14
Day 5	0.66 (0.59-0.73)	0.81 (0.75-0.86)	0.81 (0.75-0.86)	0.91
90-day Mortality				
Admission	0.85 (0.80-0.90)	0.89 (0.84-0.94)	0.92 (0.88-0.96)	**< 0.001**
Day 1	0.83 (0.77-0.89)	0.90 (0.85-0.94)	0.92 (0.88-0.96)	**< 0.001**
Day 3	0.82 (0.73-0.91)	0.90 (0.84-0.95)	0.91 (0.85-0.96)	**< 0.05**
Day 5	0.83 (0.74-0.92)	0.88 (0.83-0.93)	0.90 (0.85-0.96)	**< 0.01**

Area under the receiver operating characteristic curve (AUC) of logMRproANP alone and of different prognostic models. Model 1 includes age and 2 to 3 main predictors (congestive heart failure and atrial fibrillation (AF) for cardioembolic stroke; National Institute of Health Stroke Scale (NIHSS), total anterior circulation syndrom (TACS) and Charlson Comorbidity Index (CCI) for functional outcome; NIHSS, TACS and congestive heart failure for mortality). Model 2 includes age and the same main predictors plus logMRproANP levels on different time-points. P values indicate significance of the difference between Model 1 and Model 2 (likelihood ratio test).

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